Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400, Rm 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW March 18, 2002

NDA NUMBER 21-361

NAME OF DRUG Lumenax (Primary) and — (Alternate)
(Rifaximin Tablets) 200 mg

NDA SPONSOR Salix Pharmaceuticals, Inc

*****NOTE This review contains proprietary and confidential information that should not be released to the public *****

I INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products, for assessment of the proprietary names "Lumenax" and — ', regarding potential name confusion with other proprietary or established drug names

PRODUCT INFORMATION

Lumenax or — (rifaximin) tablets is a broad-spectrum antibiotic used to treat gastrointestinal infections Lumenax (_ —) is indicated to treat patients with traveler's diarrhea The recommended dose for Lumenax (—) is 200 mg by mouth three times daily for three days Lumenax (—) can be administered orally with or without food Lumenax —) will be available as a 200 mg oral tablet

II RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i] [ii] as well as several FDA databases[iii] for existing drug names which sound or look similar to Lumenax or — to a degree where potential confusion between drug names could occur under the usual clinical practice settings The Saegis[iv] Pharma-In-Use database was searched for drug names with potential for confusion An Expert Panel discussion was conducted to review all findings from the searches In addition, DMETS conducted six prescription analysis studies, to simulate the prescription ordering process

[i] MICROMEDEX Healthcare Intranet Series 2002 MICROMEDEX Inc 6200 South Syracuse Way Suite 300 Englewood Colorado 80111-4740 which includes the following published texts DrugDex PoisINDex Martindale (Parfitt K (Ed) Martindale The Complete Drug Reference London Pharmaceutical Press Electronic version), INDex Nominum and PDR/Physician s Desk Reference (Medical Economics Co Inc 2002)

[ii] Facts and Comparisons 2002 Facts and Comparisons St Louis MO

[iii] The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests New Drug Approvals 98 02 and online version of the FDA Orange Book

[iv] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service available at www thomson thomson com

A EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names, Lumenax and — Potential concerns regarding drug marketing and promotion related to each proposed name were also discussed This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC) The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name

1 DDMAC did not have any concerns with **Lumenax** in regard to promotional claims

2 The Expert Panel identified seven medication names that have potential for confusion with **Lumenax** These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage

Table 1 Potential sound-alike and look-alike names identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose*	Look-alike or Sound-alike
Lumenax	Rifaximin tablets 200 mg	200 mg PO three times daily for 3 days	
Lovenox	Enoxaparin sodium Injection 30 mg/0 3 mL 40 mg/0 4 mL 60 mg/0 6 mL 80mg/0 8 mL 100 mg/1 mL 90 mg/0 6 mL 120 mg/0 8 mL 150 mg/1 mL	DVT/PE treatment 1 mg/kg SC every 12 hours DVT/PE prophylaxis 30 mg every 12 hours for 7 to 10 days postoperatively	Look-alike and Sound-alike
Zovirax	Acyclovir Oral tablet 400 mg 800 mg Oral capsule 200 mg Suspension 200 mg/5 mL Powder for injection 500 mg/vial 1000 mg/vial	IV 10 mg/kg infused over 1 hour every 8 hours for 7 to 10 days PO 200 mg five times daily for 10 days	Look-alike
Luminal	Phenobarbital 130 mg/mL injection Other formulations include Oral tablets 15 mg 16 mg 30 mg, 60 mg 90 mg 100 mg Oral capsule 16 mg Elixir 15 mg/5 mL 20 mg/5 mL Injection 30 mg/mL 60 mg/mL, 65 mg/mL	SEDATION 30 to 120 mg/day PO in 2 to 3 divided doses 30 to 120 mg/day IM or IV HYPNOTIC 100 mg to 200 mg by mouth 100 mg to 320 mg IM or IV ANTICONVULSANT 60 mg to 100 mg/day by mouth, 200 mg to 320 mg IM or IV repeated every 6 hours PRN	Look-alike and Sound-alike
Lumigan	Bimatoprost 0 03% ophthalmic solution	One drop in affected eye(s) once daily in the evening	Sound-alike
Lumenhance	Manganese chloride tetrahydrate	Optimal dose has not been determined	Sound-alike
Sominex (OTC)	Diphenhydramine Oral tablet 50 mg and 25 mg	25 mg to 50 mg PO as needed for sleep	Look-alike and Sound-alike

* Frequently used not all inclusive

*****NOTE** **Proprietary and confidential information that should not be released to the public** ***

3 DDMAC did not have any concerns with — n regard to promotional claims

4 The Expert Panel identified seven medication names that have potential for confusion with — These products are listed in Table 2, along with the dosage forms available and usual FDA-approved dosage

Table 2 Potential sound-alike and look-alike names identified by DMETS Expert Panel

Product Name	Dosage form(s) Generic name	Usual adult dose	Look-alike or Sound-alike
Rifaximin	Rifaximin tablets 200 mg	200 mg PO three times daily for 3 days	
Luvox	Fluvoxamine Oral tablet 25 mg 50 mg 100 mg	Initial 50 mg PO once daily at bedtime, titrate to 100 mg to 300 mg/day	Look-alike and Sound-alike
Lonox	Diphenoxylate and atropine sulfate Oral tablet 2 5 mg/0 025 mg Other formulations (non-Lonox) include Oral liquid 2 5 mg/0 025 mg per 5 mL	Initial dose is 5 mg four times daily	Look-alike and Sound-alike
Flomax	Tamsulosin Oral capsule 0 4 mg	0 4 mg PO once daily	Look-alike and Sound-alike
Bumex	Bumetanide Oral tablets 0 5 mg 1 mg 2 mg Injection 0 25 mg/mL	ORAL 0 5 mg to 2 mg PO once daily max is 10 mg IV or IM 0 5 mg to 1 mg once May repeat as needed	Look-alike and Sound-alike
Eurax	Crotamiton 10 % Cream 10 % Lotion	Massage into affected areas as needed	Look-alike
Xanax	Alprazolam Oral tablet 0 25 mg 0 5 mg 1 mg 2 mg Oral solution 0 5 mg/5 mL	0 25 mg to 0 5 mg PO three times daily	Look-alike

* Frequently used not all inclusive

***NOTE **Proprietary and confidential information that should not be released to the public** ***

B PRESCRIPTION ANALYSIS STUDIES

1 Methodology for **Lumenax** studies

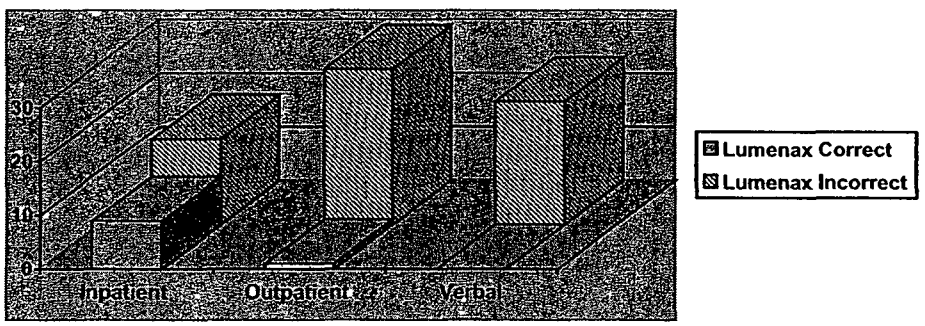
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Lumenax with other U S drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name These studies employed a total of 113 health care professionals (nurses, pharmacists, and physicians) This exercise was conducted in an attempt to simulate the prescription ordering process DMETS staff members wrote inpatient and outpatient prescriptions for Lumenax, each consisting of a combination of marketed and unapproved drug products These written prescriptions were optically scanned and one prescription was delivered via email to each study participant In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail Each reviewer was then requested to provide an interpretation of the prescription via email

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Lumenax	
Inpatient Lumenax x tid x 3 days bid	*Verbal* Lumenax Three times daily for three days
Outpatient Lumenax Tid x 3 days	

2 Results for Lumenax studies

Results of these exercises are summarized below

Study	No. of participants	# of responses (%)	"Lumenax" response	Other response
Written Inpatient	34	25 (74%)	9 (36%)	16 (64%)
Written Outpatient	40	30 (75%)	1 (3%)	29 (97%)
Verbal	39	23 (59%)	0 (0%)	23 (100%)
Total	113	78 (69%)	10 (13%)	68 (87%)



Among the two written prescription studies, 45 of 55 (82 %) participants interpreted the name incorrectly The most common misinterpretations were *Lamenax* and *Lumena* Other incorrect responses included *Lamenox, Laminax, Laminex, Lumen, Lumenex,* and *Lumenox*

Among the verbal prescription study participants for Lumenax — 23 of 23 (100 %) participants interpreted the name incorrectly However many of the incorrect responses were phonetically equivalent to Lumenax These responses included *Luminax* and *Luminex* Other misinterpretations included *Ruminax, Ruminex, Reuminex, Rheumadex, Rheumanex, Rheumenex, Rheumomax* and *Rumenax*

3 Methodology for — studies

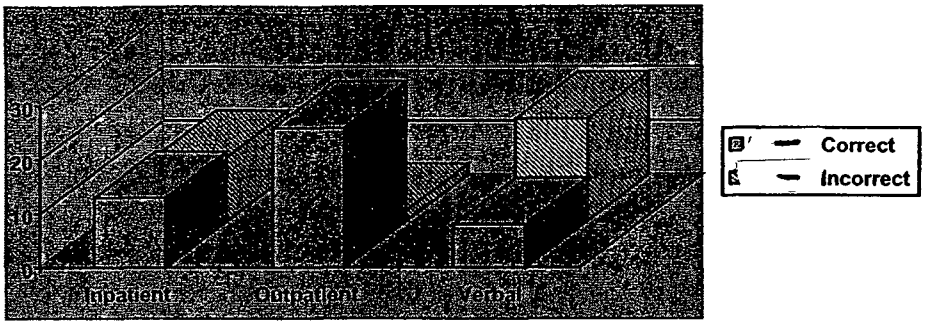
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of — with other U S drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name These studies employed a total of 108 health care professionals (nurses, pharmacists, and physicians) This exercise was conducted in an attempt to simulate the prescription ordering process DMETS staff members wrote inpatient and outpatient prescriptions for — , each consisting of a combination of marketed and unapproved drug products These written prescriptions were optically scanned and one prescription was delivered via email to each study participant In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail Each reviewer was then requested to provide an interpretation of the prescription via email

HANDWRITTEN PRESCRIPTIONS —	VERBAL PRESCRIPTION
Inpatient [illegible]	*Verbal* / 1 tablet PO TID for three days Dispense number nine
Outpatient / #9 Sig: 1 tab TID x 3 days	

4 Results for — studies

Results of these exercises are summarized below

Study —	No. of participants	# of responses (%)	— response	Other response
Written Inpatient	36	25 (69%)	13 (52%)	12 (48%)
Written Outpatient	33	28 (85%)	26 (93%)	2 (7%)
Verbal	39	27 (69%)	8 (30%)	19 (70%)
Total	108	80 (74%)	47 (59%)	33 (41%)



Among the two written prescription studies, 14 of 53 (26 %) participants interpreted the name incorrectly The most common misinterpretations were *Lumox* and *Luvox* Other incorrect responses included *Lumat, Luwax, Lurax, Lurivax, Lurmax, Lurvax* and *Luvanax*

Among the verbal prescription study participants for Lumenax — , 19 of 27 (70 %) participants interpreted the name incorrectly The most common misinterpretations were *Lomax* and — Other incorrect responses included *Lomex, Numax, Nomax* and *Neumax*

C SAFETY EVALUATOR RISK ASSESSMENT

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1 Risk assessment for **LUMENAX**

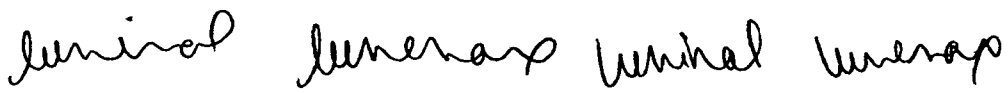
In reviewing the proprietary name, Lumenax, the primary concerns raised by the expert panel were related to several proprietary names (see Table 1) that already exist in the US marketplace We conducted prescription studies to simulate the prescription ordering process There was no confirmation that Lumenax could be confused with Lovenox, Zovirax, Luminal, Lumigan, Lumenhance, — or Sominex However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size

Lovenox has potential for look-alike and sound-alike confusion with Lumenax These names begin and end with the same letters and contain the same number of syllables and letters, which increases the likelihood for confusion When handwritten, "LOVE-" can look similar to "LUME-" as does "-NOX" and "-NAX" Lovenox is used to treat a different condition than Lumenax and it is an injectable medication, unlike Lumenax Although the dosage strengths for Lovenox do not overlap with Lumenax, it would be possible to use two 100 mg/mL prefilled syringes to equal the 200 mg dose of Lumenax, in error Both Lumenax and Lovenox can be used for a short course of therapy It is also possible that Lovenox and Lumenax will be stored near each other in some pharmacies

lovenox lumenax

Zovirax has potential for look-alike confusion with Lumenax Zovirax is available as a 200 mg oral capsule, similar to Lumenax Both medications are used to treat infections and require a short course of treatment Lumenax and Zovirax could be prescribed by the same type of specialist Although the dosing schedule for Zovirax is different from Lumenax, both medications are administered multiple times daily

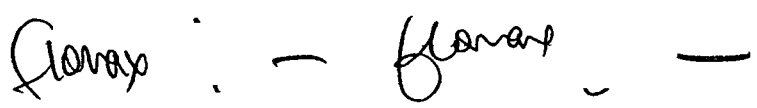
Luminal has potential for look-alike and sound-alike confusion with Lumenax "LUMIN-" and "LUMEN-" have the same sound, differ by only one letter and "I" and "E" can also look the same The endings "-AL" and "-AX" can look similar when handwritten The sound-alike similarity also comes from the same number of syllables in the names Luminal is used to treat different conditions than Lumenax Although there is no 200 mg dosage strength of phenobarbital or Luminal, it is possible to make a 200 mg dose from two 100 mg oral tablets Luminal is used in a different patient population than Lumenax and it would be prescribed by a different specialist Additionally, Luminal is a proprietary name for phenobarbital, which is available from various generic manufacturers in numerous dosage formulations Therefore the risk for confusion is minimized because the established name (phenobarbital) is likely used more often than "Luminal" when this product is prescribed or dispensed



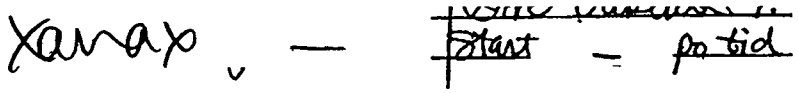
Lumigan has potential for sound-alike confusion with Lumenax Lumigan is an ophthalmic solution used to treat conditions of the eye, unlike Lumenax There is no overlap in dosage strength and it is unlikely that Lumigan will be stored near Lumenax which minimizes the likelihood for confusion

Lumenhance has potential for sound-alike confusion with Lumenax Lumenhance is used as a diagnostic agent for imaging studies of the gastrointestinal tract Because the context of use is very different from Lumenax, the risk for confusion is minimized Further, it is unlikely that these products will be stored near one another

Flomax has potential for look-alike and sound-alike confusion with — Flomax is used to treat signs and symptoms of benign prostatic hyperplasia, unlike — Although Flomax is available as 0 4 mg oral capsules, it is possible for prescribers to omit the dosage strength for — and Flomax because both are only available as a single strength Flomax is used to treat a male patient population for a chronic condition, while — is used to treat a general adult population for an acute/episodic condition The risk for confusion is minimized because the context of use for Flomax greatly differs from —

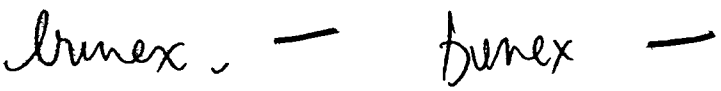


Xanax has look-alike similarity to — which is based mostly on the ending letter combinations of "-anax" and — Xanax is available in different dosage strengths and used to treat a different condition than — However, both medications are administered on a three times daily dosing schedule and are available as oral solid dosage forms



Eurax looks similar to — when handwritten The letters "e" and "l" can be confused Additionally, "-urax" and — look the same However, Eurax is available as a topical cream or lotion unlike — Eurax is used for a short course of therapy to treat scabies infestations Comparatively, — is used for a short course of therapy to treat infections of the gastrointestinal tract, including traveler's diarrhea Eurax is administered on a different schedule than — Eurax and — are not likely to be stored near one another in a pharmacy Although there are some differences between the products, these names are very similar and confusion is likely

Bumex can look and sound similar to — Lowercase "l" and "b" letters look similar as does the "-umex" and — These names also share the same number of syllables and have the same number of letters However, Bumex is used to treat a different condition and has different dosage strengths and a different dosing schedule than — minimizing the likelihood for confusion



In addition to potential for look-alike and sound-alike confusion with the names described above, there is potential for confusion related to the packaging configuration of Lumenax The sponsor proposes

III COMMENTS TO BE PROVIDED TO THE SPONSOR

DMETS does not recommend use of the proprietary names, Lumenax or This recommendation is based on the reasons described below

Risk Assessment for **LUMENAX**

Lovenox has potential for look-alike and sound-alike confusion with Lumenax These names begin and end with the same letters and contain the same number of syllables and letters, which increases the likelihood for confusion When handwritten, "LOVE-" can look similar to "LUME-" as does "-NOX" and "-NAX" Lovenox is used to treat a different condition than Lumenax and it is an injectable medication, unlike Lumenax Although the dosage strengths for Lovenox do not overlap with Lumenax, it would be possible to use two 100 mg/1 mL prefilled syringes to equal the 200 mg dose of Lumenax, in error Both Lumenax and Lovenox can be used for a short course of therapy Lovenox is used in a different type of patient population and is typically prescribed by a different type of specialist than Lumenax It is possible that Lovenox and Lumenax will be stored near each other in some pharmacies

lovenox lumenax

Zovirax has potential for look-alike confusion with Lumenax Zovirax is available as a 200 mg oral capsule, similar to Lumenax Both medications are used to treat infections and require a short course of treatment Lumenax and Zovirax could be prescribed by the same type of specialist Although the dosing schedule for Zovirax is different from Lumenax, both medications are administered multiple times daily

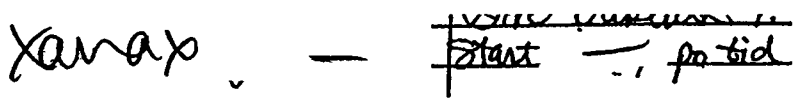
Risk Assessment for ___

Luvox has potential for look-alike and sound-alike confusion Luvox and — start and end with the same letters, share the same number of syllables and have the same number of letters, which contributes to their look-alike and sound-alike similarity Although there is no overlap in the dosage strengths, it would be possible to use two 100 mg Luvox tablets to equal a 200 mg dose of — Luvox is used to treat a different condition and is used on a more chronic basis, unlike — Luvox has a different dosing schedule and us prescribed by a different type of specialist However, Luvox and — could be stored near one another on a pharmacy shelf Although there are many different factors, the names are very similar and confusion is likely

Lonox has look-alike and sound-alike similarity to — Lonox and — start and end with the same letters, share the same number of syllables and have the same number of letters, which contributes to their look-alike and sound-alike similarity Additionally, the letters "a', "o" and "u" can look similar when handwritten, as does "m" and "n" Lonox is a combination product that is used to treat a different condition than — Although Lonox is administered on a different dosing schedule than — they are both dosed multiple times daily and Lonox could be stored near each other on the pharmacy shelf, increasing the likelihood for confusion

Flomax has potential for look-alike and sound-alike confusion with — Flomax is used to treat signs and symptoms of benign prostatic hyperplasia, unlike — Although Flomax is available as 0 4 mg oral capsules, it is possible for prescribers to omit the dosage strength for — and Flomax because both are only available as a single strength Flomax is used to treat a male patient population for a chronic condition, while — is used to treat a general adult population for an acute/episodic condition The risk for confusion is minimized because the context of use for Flomax greatly differs from —

Xanax has look-alike similarity to — which is based mostly on the ending letter combinations of "-anax" and " — " Xanax is available in different dosage strengths and used to treat a different condition than — However, both medications are administered on a three times daily dosing schedule Although Xanax and — are both available as oral solid dosage forms, it is unlikely that they would be stored near each other



Eurax looks similar to — when handwritten The letters "e" and "l" can be confused Additionally, "-urax" and " — look the same However, Eurax is available as a topical cream or lotion unlike — Eurax is used for a short course of therapy to treat scabies infestations Comparatively, — is used for a short course of therapy to treat infections of the gastrointestinal tract, including traveler's diarrhea Eurax is administered on a different schedule than — Eurax and — are not likely to be stored near one another in a pharmacy Although there are some differences between the products, these names are very similar and confusion is likely

In addition, DMETS has reviewed the draft container label, draft carton labeling, insert labeling and patient information leaflet for Lumenax " — and has attempted to focus on safety issues relating to possible medication errors We have identified areas of possible improvement, in the interest of minimizing potential user error

A GENERAL COMMENT

It is not possible to fully assess the safety of the labels and labeling because the information provided did not reflect the label and labeling presentation that will actually be used on the marketplace (i e color, placement of name, etc) Please forward copies of the final printed labels and labeling when they are available

B " — CONTAINER LABEL

C LABELING

D CONTAINER LABELS

See comments above

E PROFESSIONAL SAMPLE

F INSERT LABELING

1 Clarify the HOW SUPPLIED section for the configuration

2 Clarify the meaning of

IV RECOMMENDATIONS

A DMETS does not recommend the use of the proprietary name "Lumenax"

B DMETS does not recommend the use of the proprietary name —

C DMETS recommends implementation of the labeling and packaging revisions described in Section III Please forward copies of the final printed labels and labeling when they are available

DMETS would appreciate feedback of the final outcome of this consult (e g , copy of revised labels/labeling) We are willing to meet with the Division for further discussion as well If you have any questions concerning this review, please contact
Sammie Beam at 301-827-3242

_____

Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)

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/s/

Marci Ann Lee
5/2/02 12 44 54 PM
PHARMACIST

Carol Holquist
5/2/02 01 06 55 PM
PHARMACIST

Jerry Phillips
5/6/02 08 59 39 AM

Minutes of a Teleconference

Date January 16, 2002

Application NDA 21-361
Lumenax (rifaximin) Tablets

Sponsor Salix Pharmaceuticals, Inc

Participants

Salix Pharmaceuticals, Inc

Alvaro Carvajal	Vice President, Information Systems
Allen Mangel, M D	Vice President, Research and Development
Lorin Johnson, Ph D	Senior Vice-President and Chief Scientific Officer

Salix Pharmaceuticals, Inc Consultants

	Statistician
	SAS Programmer
	Database Programmer
	Regulatory Affairs

FDA

Edward Cox, M D	Acting Team Leader/Medical, HFD-590
Regina Alivisatos, M D	Medical Officer, HFD-590
Cheryl Dixon, Ph D	Statistician, HFD-725
Diana Willard	Regulatory Health Project Manager, HFD-590

Background

NDA 21-361 was submitted on December 21, 2001 for the treatment of traveler's diarrhea Included in the December 21, 2001 submission were clinical datasets in SAS XPORT Transport format As Dr Alivisatos began her review, several questions regarding the database arose This teleconference was requested by the Division to address Dr Alivisatos' questions regarding the electronically formatted clinical datasets

Discussion

Following introductions, Dr Alivisatos stated that while she understands that there are two investigators and two sites for Study RFID9701, from the presentation of the data in the electronic data sets, it appears that there are two sites and only one investigator, i e , the codes "J1" and "M1 " Mr Carvajal stated that the "M" is for Mexico, the "J" for Jamaica, and that the

"1" in the INVNO column is probably not needed in this particular dataset as each country has only one investigator, Dr DuPont in Mexico and Dr — in Jamaica Mr — noted that Dr Alivisatos had requested a list of patients at these two distinct clinical sites and indicated that such a list will be submitted to the NDA

Dr Alivisatos asked why investigator number "4" appears, from her cursory review of the electronic submission, only in the laboratory datasets Mr Carvajal stated that the number "4" was used only in the laboratory datasets in the field named INVO INVO was defined as the clinical laboratory site For study RFID9701, clinical site "1' is in Guadalajara, Mexico and clinical site "4" is in Morelia, Mexico Dr Cox stated that the name INVO for the clinical laboratory sites in the laboratory dataset could lead to confusion and perhaps a name such as LAB ID would have been more indicative of the data in this field Salix included the INVO field in the dataset in order to identify the different reference ranges among the different laboratories The sponsor indicated that definitions regarding these names were not submitted in the data dictionary

Mr Carvajal noted that the Division had requested in August of 2001 that information regarding the investigators be added to the datasets As the datasets were relatively complete at that point in time this information was added at the end of the data entering process after the data validation Mr Carvajal further noted that this was the only change made after the initial validation In response to a query from Dr Cox, Mr Carvajal stated that Salix is not aware of any other issues similar to this in the datasets

Salix offered to provide a revised file for Study RFID9701 that would identify the Mexican clinical study sites as well as the Jamaican site Salix agreed to validate the datasets before submitting it to the NDA Salix further stated that their goal would be to submit the revised file for Study RFID9701 by Tuesday, January 22, 2001 as Mr Carvajal has already made arrangements to meet with Dr Alivisatos to aid in loading the Access Viewers and could merge this revised file with that in the original submission and then validate the datasets

Summary

Dr Alivisatos' questions regarding coding and formatting in the clinical datasets were discussed Salix offered to provide a revised dataset for Study RFID9701 If the revised dataset is completed before Mr Carvajal's already arranged January 22, 2002 meeting with Dr Alivisatos to assist in loading the Access Viewers, Mr Carvajal will also submit the revised datasets If the datasets are not ready for submission, the meeting with Dr Alivisatos will be re-scheduled

Minutes Preparer _____
Diana Willard
Regulatory Health Project Manager

Concurrence, Meeting Chair _____
Edward Cox, M D
Acting Medical Team Leader, HFD-590

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/s/

Diana Willard
2/15/02 01 25 43 PM
CSO

Edward Cox
2/21/02 01 15 42 PM
MEDICAL OFFICER

Memorandum of a Teleconference

Meeting Date	December 7, 2001
Application	IND 52,980 rifaximin tablets
Sponsor	Salix Pharmaceuticals, Inc
Subject	Discussion of rifaximin data for NDA submission

Attendees

Salix Pharmaceuticals, Inc

Allen Mangel, M D , Ph D	Vice-President, Research and Development
Joe Tyler, Ph D	Vice-President, Operations
Lorin Johnson Ph D	Sr Vice-President and Chief Scientific Officer

Salix Pharmaceuticals, Inc Consultants

	Regulatory Affairs,
	Clinical,
	Preclinical
	Regulatory Affairs, Pharmacokinetics

FDA

Renata Albrecht, M D	Acting Division Director, HFD-590
Edward Cox, M D	Medical Officer/Acting Team Leader, HFD-590
John Powers, M D	Medical Officer, HFD-590
Karen Higgins, Sc D	Statistics/Team Leader, HDF-725
Shukal Bala, Ph D	Microbiology/Team Leader, HFD-590
Steve Kunder, Ph D	Pharmacology/Toxicology Reviewer, HFD-590
Diana Willard	Regulatory Health Project Manager, HFD-590

Background

During the January 12, 2001 pre-NDA meeting for rifaximin, the Division recommended that Salix Pharmaceuticals, Inc (Salix) submit, when available, updated clinical microbiological data On November 2, 2001, Salix submitted pooled microbiology data from the three infectious diarrhea studies (Study RFID9601, Study RFID9701, and Study RFID9801) In this submission, Salix also requested a teleconference with the Division to discuss these results prior to the planned December 2001 submission date for the rifaximin NDA

IND 52 980
December 7, 2001

A December 3, 2001 facsimile transmission from Salix contained a proposed indication for rifaximin tablets as follows

INDICATIONS AND USAGE LUMENAX™ Tablets are indicated for the treatment of patients (≥ 12 years of age) with traveler's diarrhea caused by — *Escherichia coli*

/

Discussion

Following introductions, Mr — stated that at the January 12, 2001 pre-NDA meeting for rifaximin, Dr Goldberger had recommended that Salix share updated clinical microbiological data with the Agency prior to submission of a NDA for rifaximin Dr Cox responded that the Division staff had reviewed the November 2 2001 submission containing these updated data in preparation for this teleconference

Dr Powers further noted that at the pre-NDA meeting, Dr Goldberger stated that the Division would expect the clinical and microbiological data in the NDA to include data on patients infected with a variety of organisms implicated as causes of diarrheal illness Diarrhea is an empirically treated disease caused by various organisms depending on geographic location of travel as well as the season of travel Our current guidance recommends that drug sponsors submit a minimum of 10 evaluable patients with each of the common organisms implicated in traveler's diarrhea, including *Campylobacter* species The six isolates of *Campylobacter* species submitted in the November 2, 2001 package falls short of this recommended guideline In addition, Salix should provide data showing that the *in vitro* activity of rifamixin is similar across species within a genus in which the clinical disease is similar For example, the activity of rifaximin should be similar against *Shigella flexneri* and *Shigella sonnei* which cause a similar diarrheal illness (as opposed to the different clinical disease caused by typhoidal vs non-typhoidal strain of *Salmonella*) Salix should also provide data that shows that the in vitro activity of rifaximin is similar in isolates from different geographic locales

The Division stated that Salix should submit data from an adequate number of patients infected with each genus/species of organism AND treated with the dose of rifaximin for which Salix is seeking approval Dr Cox emphasized that data from a minimum of 10 patients refers to **evaluable** patients, not merely all enrolled patients infected with a given type of organism Patients may not be evaluable for various reasons such as administration of concomitant antimicrobials or anti-motility agents, which would lower the number of isolates for each organism The Division requested that Salix provide data on the numbers of isolates in patients treated at each dosing level of rifaximin

Salix asked if the Agency would consider the submission of a *Campylobacter* report as a major amendment during the review of the rifaximin NDA Dr Albrecht stated that since 1992, following enactment of the Prescription Drug User Fee Act, the Agency reviews an application within 60 days of its receipt to determine if it is adequate for review While the Division may be able to say that a rifaximin NDA is adequate for review,

Dr Albrecht stated that Salix should be aware that the Division currently has questions regarding dosing regimens, [redacted] These concerns make it difficult to discuss the submission of additional data at this point in time Dr Albrecht also noted that the workload of the Division at the time of the submission of the major amendment may not allow the Division to review the amendment within that review cycle Dr Albrecht also noted that Salix would also be assuming the risk that any additional studies would be completed within the review time for the original NDA submission

Before taking an action on a rifaximin NDA, the Division will also consider the efficacy of rifaximin in relation to placebo, i e , the cure rate in rifaximin would need to exceed placebo taking into account the possibility that the placebo cure rate may be high

[redacted]

Summary

Issues pertaining to the November 2, 2001 submission containing pooled microbiology data from the three rifaximin infectious diarrhea studies were discussed The Division outlined their concerns regarding numbers of evaluable patients [redacted] at the dose chosen for the label [redacted]

Minutes Preparer _____
Diana Willard
Regulatory Health Project Manager

Concurrence, Meeting Chair _____
Renata Albrecht, M D
Acting Division Director, HFD-590

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/s/

Renata Albrecht
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Memorandum of a Teleconference

Meeting Date August 24, 2001

Application IND 52,980
rifaximin tablets

Sponsor Salix Pharmaceuticals, Inc

Subject Electronic submission for rifaximin

Attendees

Salix Pharmaceuticals, Inc

Alvaro Carvajal Vice President, Information Systems

Salix Pharmaceuticals, Inc Consultant

[redacted], Regulatory Affairs

FDA

Brad Leissa, M D	Medical Officer/Team Leader, HFD-590
Randy Levin, Ph D	Associate Director, Electronic Review
John Powers, M D	Medical Officer, HFD-590
Diana Willard	Regulatory Health Project Manager, HFD-590

Background

During an April 6, 2001 pre-NDA meeting held to discuss the electronic submission for rifaximin, Dr Powers requested that Salix Pharmaceuticals, Inc (Salix) submit a clinical dataset containing "dummy" data in SAS XPORT Transport format This SAS XPORT Transport data was submitted to IND 52,980 on July 25, 2001 This July 25, 2001 submission states that, based on conversations with Dr Levin in May and June of 2001, Salix determined that the Microsoft ACCESS database and a case report form (CRF) type viewer Review Aid as proposed at the January 12 and April 6, 2001 Pre-NDA meetings, would not be included in the NDA submission for rifaximin

The Division requested this teleconference to clarify the Agency's position on inclusion of the Microsoft ACCESS database and a CRF type viewer Reviewer AID in the rifaximin NDA

Discussion

Dr Leissa stated that this teleconference was requested by the Division to discuss the statement in Salix's July 25, 2001 submission to IND 52,980 regarding submission of a Microsoft ACCESS database in the rifaximin NDA In this submission, Salix states that,

based on conversations with Dr Levin in May and June of 2001, Salix decided that the Microsoft ACCESS database and a CRF type viewer Reviewer Aid would not be included in the rifaximin NDA submission

Subsequent to Salix's conversations with Dr Levin, the issue of submission of the Microsoft ACCESS database with the rifaximin NDA was discussed internally FDA's understanding of why Salix decided not to include the ACCESS viewers is because the ACCESS database is not archivable and due to the need to provide validation documentation for the ACCESS viewers Salix agreed with FDA's understanding of the issues

Dr Levin clarified that it is only the source data that need to be archivable Dr Leissa proposed that Salix provide the SAS XPORT formatted file and the ACCESS viewers to the Agency The Agency would then be responsible for validating the output from these files thus eliminating the concern about validating the ACCESS viewers

Salix and the Agency agreed on the following

- Salix will submit the SAS XPORT file, batch files for transferring SAS files to ACCESS, and an empty ACCESS viewer database and viewer files
- The Agency will populate the ACCESS viewer files from SAS
- The Division will be responsible for any validation associated with the use of the Microsoft ACCESS database and a CRF type viewer

Mr Carvajal stated that Salix could provide these data, for both safety and efficacy, in the NDA submission for the three infectious diarrhea studies as this work was completed before the conversations with Dr Levin However, subsequent to the May and June 2001 conversations with Dr Levin, Salix ceased work on these data for the hepatic encephalopathy (HE) studies Noting that the target date for the submission of the rifaximin NDA is November 2001, Dr Leissa asked if it would be possible for Salix to provide the HE data soon after the original NDA submission Mr —— stated that Salix will discuss the issue of the HE data internally and then advise the Division of when the HE Microsoft ACCESS database and a CRF type viewer could be submitted For the HE studies, only safety data would be available as the studies are on-going

Mr Carvajal added that the formatting of the SAS XPORT files will be identical to that submitted on July 25, 2001

The August 23, 2001 Facsimile Transmission to IND 52,980

An August 23, 2001 facsimile transmission to Salix regarding the July 25, 2001 submission to IND 52,980 contained the following three comments

- Please clarify the purpose/function of the COMMENTS dataset

- Please provide the patient identification number, the investigator identification number, and the treatment received in every dataset

- Wherever microbiologic data are presented in a dataset, please identify the species

Mr [redacted] stated that the COMMENTS dataset is a duplicate of the Define PDF file and was inadvertently included in the SAS XPORT transport files It will not be included in the final SAS XPORT transport files The information requested in Item 2 by the statistician will be provided Regarding Item 3, the NDA will contain species information for the microbiologic data Dr Leissa noted that this last item is important as labeling will be written at the species level

Mr [redacted] added that the programming language used to generate tables will be provided in the NDA submission Dr Leissa stated that that information would be helpful to the statisticians

Minutes Preparer _____
Diana Willard

Concurrence, Meeting Chair _____
Brad Leissa, M D

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/s/

Diana Willard
9/24/01 08 15 10 AM
CSO

Brad Leissa
9/24/01 01 00 34 PM
MEDICAL OFFICER

Minutes of a Meeting

Meeting Date	April 6, 2001
Application	IND 52,980 rifaximin tablets
Sponsor	Salix Pharmaceuticals, Inc
Subject	Pre-NDA/Electronic Submission

Attendees

Salix Pharmaceuticals, Inc

Lise Riopel, Ph D	Vice President, Clinical Affairs
Alvaro Carvajal	Vice President, Information Systems

Salix Pharmaceuticals, Inc Consultants

—	Regulatory Affairs Consultant

FDA

Brad Leissa, M D	Team Leader/Medical Officer, HFD-590
John Powers, M D	Medical Officer, HFD-590
Karen Higgins, Sc D	Team Leader/Mathematical Statistician, HFD-725
Cheryl Dixon, Ph D	Statistician, HFD-725
Philip Colangelo, Ph D	Clinical Pharmacology & Biopharmaceutics, HFD-880
Houda Mahayni, Ph D	Clinical Pharmacology & Biopharmaceutics, HFD-880
Peter Dionne, M S	Microbiologist, HFD-590
Shukal Bala, Ph D	Team Leader/Microbiology, HFD-590
Steve Kunder, Ph D	Pharmacologist, HFD-590
Diana Willard	Regulatory Health Project Manager, HFD-590

Background

This Pre-NDA meeting was requested by Salix Pharmaceuticals, Inc (Salix) to discuss issues regarding the electronic submission for their proposed NDA for rifaximin tablets for the treatment of infectious diarrhea The sponsor submitted a meeting package on March 22, 2001 in preparation for this meeting

Meeting Objective

The meeting objectives were

- to familiarize the Division with the electronic submission,
- to identify any issues concerning the proposed format of the electronic submission,
- to ensure the documents standards are acceptable to the Division, and
- to identify additional features that will assist the reviewers

Discussion

Following introductions, Salix presented slides (Attachment 1) and the following issues were discussed

Adminstrative

- The current timeline for submission of a rifaximin NDA is the 4th quarter of 2001, most probably October 2001
- Salix stated that any document currently in a foreign language will be translated to English for the NDA submission
- Dr Leissa suggested that Salix set up a secure E- mail link with the Division to allow for encrypted E-mail to be exchanged during the NDA review

Formatting of the Electronic Submission

- Data sets will be provided in SAS 6 12 export file format This is consistent with the guidance for providing regulatory submissions in electronic format
- Each discipline, i e , clinical, pharmacology/toxicology, chemistry, etc , will have a separate folder within the electronic submission
- Salix proposes to present documents in the electronic submission in Adobe Acrobat 4 PDF format Adobe Acrobat 3 is what is recommended in the guidance for providing regulatory submissions in electronic format Dr Leissa recommended that Salix contact CDER electronic document room personnel to ensure that Adobe Acrobat 4 PDF format is acceptable
- The guidance for industry regarding providing regulatory submissions in electronic format recommends one PDF file for reports and another PDF file for

the corresponding listings Salix agrees that two files make sense for studies that enroll thousands of patients As the rifaximin studies are relatively small, Salix proposes to provide the study reports and the corresponding listings in one electronic file in the NDA This is acceptable to the Division.

- The electronic submission will have the ability to link from an individual patient reference in a report to images for that patient in the Case Report Forms (CRFs)

- Salix stated that SAS data sets were used to key in the Access data sets

- Salix proposes to provide a viewer tool in the electronic submission for ease of using the efficacy and safety databases Dr Leissa recommended that Salix contact CDER technical staff regarding the suitability of this proposal for CDER systems In addition, Salix should consider if this tool would add any value for the reviewer over SAS and JMP capabilities

- Dr Leissa recommended that Salix send a facsimile transmission (FAX) to the Division regarding the proposed hardware and software for the rifaximin NDA This FAX will be provided to CDER information technology (IT) staff to determine if CDER can support the proposed rifaximin electronic submission

Pharmacology/Toxicology

- On page 6 of the March 22, 2001 meeting package, there is a statement that electronic data sets for animal studies will not be provided The sponsor clarified that SAS data sets for the pharmacology/toxicology studies will not be provided Individual animal data will be provided in the electronic submission in PDF format

- Data will be provided in SAS data sets in place of case report tabulations The Division stated that this is acceptable

Clinical Pharmacology & Biopharmaceutics

- On page 6 of the March 22, 2001 meeting package, there is a statement that electronic data sets for pharmacokinetic studies involving volunteers will not be included but that these data will be included with the final reports Salix clarified that most of the pharmacokinetic studies to be included in the NDA were conducted many years ago by other companies in partnership with Salix While a detailed listing of patients versus normal subjects is included in PDF format for almost all of the studies to be included in the NDA as part of the study reports, these data are not available in SAS The NDA will include pharmacokinetic reports from studies conducted in 1983 in France Final study reports for these French studies will be scanned using an OCR program The electronic sources for the pharmacokinetic studies conducted in 1984-1985 are available and data from

those studies will be presented in the NDA in PDF format Data from the food effect study conducted by Salix will be submitted as SAS transport files

Dr Mahayni stated that it would be useful to submit any urine concentration and plasma concentration data that are obtainable Mr stated that Salix will review with their partners that conducted the pharmacokinetic studies what, if any, concentration data are available to submit in the NDA

- Dr Colangelo requested that, if possible, the pharmacokinetic parameter data be submitted in ASCI format rather than in SAS The ASCI data sets should not be delineated by any hard spaces

- Salix stated that pharmacokinetic reports are hyper-linked to individual data

- Dr Mahayni requested that the pharmacokinetic synopsis be provided as a review aid in Microsoft Word

- Two studies requested during the pre-NDA meeting, the cytochrome P450 and human liver induction studies, are nearing completion and will be submitted to the IND when finalized

Clinical

- Salix stated that to review data such as liver function tests for a number of patients, the reviewer will need to utilize the SAS data sets

- Salix stated that it would be possible to create a menu in the electronic submission that would enable reviewers to link all available data for each individual patient Dr Powers stated that access to all data for a single patient in one place would be a useful tool in order to validate a single patient

- A data dictionary that defines terms used in the NDA will be provided

- As will be explained in the reviewers' guide, Study RFHE9701 is the only study without a designated area on the CRF for investigator comments If an investigator writes a comment on the CRF, however, the reviewer will be able to see the comment on the scanned CRF Salix noted that the individual patient summaries will also provide information, such as why a patient is unevaluable, for each patient

- Dr Powers requested a CD-ROM containing dummy data sets be submitted to the Division The purpose of providing the reviewers with this CD-ROM is to assess how the actual data is structured and thereby assess the ease of querying the database

Salix indicated that a CD-ROM containing dummy data sets should be available within 3-4 weeks Dr Leissa recommended that when Salix submits this CD-ROM that a timeframe for receiving comments from the Division be provided

- Salix stated that all study reports, the package insert, the ISS, and the ISE will be provided in Microsoft Word Dr Powers requested that protocols also be provided in Microsoft Word as reviewers aids

- Salix plans to submit data from studies RFHE9702 and RFHE9701 for hepatic encephalopathy in the rifaximin — diarrhea NDA —

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Microbiology

- Mr Dionne requested that a patient line listing be provided in the microbiology section This listing should include patient ID numbers, organism cultured, MICs for rifaximin and the comparator, clinical outcome, and bacteriological outcome Patient treatment should also be indicated

- Dr Bala requested that when a dummy data set containing clinical data is submitted that some microbiological data be included on the CD-ROM

- Mr Dionne noted that in the microbiology section there are data pertaining to *H pylori* and other organisms Dr Leissa stated that if there is no intent to write something into the package insert regarding *H pylori* or these other organisms, then there is no need to submit these data in the microbiology section These data would be needed only for the safety review Salix stated that the only indication planned for this NDA submission is — diarrhea The purpose for submitting these data is simply to disclose all rifaximin data that are available for all organisms

Summary

Salix presented slides and discussed reviewer concerns pertaining to the electronic submission for the upcoming rifaximin NDA

Salix will provide the Division with a CD-ROM containing dummy data sets so that the reviewers can review the structure of the SAS data sets

Salix will send the Division a FAX outlining the hardware and software proposed for the rifaximin NDA The Division will share this FAX with CDER IT personnel The Division will convey any comments from CDER IT staff to Salix

Minutes Preparer _____
Diana Willard

Concurrence, Meeting Chair _____
Brad Leissa, M D

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/s/

Diana Willard
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Brad Leissa
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Memorandum of a Teleconference

Meeting Date	January 19, 2001
Application	IND 52,980 rifaximin tablets
Sponsor	Salix Pharmaceuticals, Inc
Subject	Ciprofloxacin formulations used in rifaximin studies

Attendees

Salix

Lorin Johnson, Ph D	Senior Vice President, Development and Chief Scientific Officer
Lise Riopel, Ph D	Vice President, Clinical Affairs
John de la Fuente	Director, Quality Affairs
	Medical Consultant
	Biopharmacuetics Consultant
	Non-clinical Safety Consultant
	Regulatory Affairs Consultant
	Regulatory Affairs Consultant
	Regulatory Affairs Consultant

FDA

Funmilayo Ajayi, Ph D	Team Leader/Clinical Pharmacology & Biopharmaceutics, HFD-880
Houda Mahayni, Ph D	Clinical Pharmacology & Biopharmaceutics, HFD-880
Diana Willard	Regulatory Health Project Manager, HFD-590

Background

The Division requested this teleconference to clarify Salix's proposal, as discussed during the January 12, 2001 pre-NDA meeting for rifaximin, to establish bioequivalency between the U S Bayer ciprofloxacin formulation and the ciprofloxacin formulation used in Study R/C-TD/01 97 The sponsor plans to submit the report of a bioequivalence study comparing the generic ciprofloxacin tablets manufactured in Spain to the Spanish Bayer tablet formulation and a report of an *in vitro* dissolution study comparing the Spanish Bayer formulation to the US Bayer formulation

Discussion

Dr Ajayi noted that in Question 2 of the December 15, 2000 pre-NDA meeting package, Salix asked if their proposal to establish *in vivo* bioequivalency between the U S Bayer ciprofloxacin formulation and the Spanish generic ciprofloxacin formulation used in Study R/C-TD/01 97 with comparative dissolution data is acceptable

Ms [redacted] stated that the manufacturer of the Spanish generic ciprofloxacin formulation conducted an in-vivo bioequivalence study comparing their generic version of ciprofloxacin tablets to the Bayer ciprofloxacin tablet formulation approved in Spain In order to establish bioequivalency of the generic ciprofloxacin manufactured in Spain and the Spanish Bayer formulation to the approved U S Bayer ciprofloxacin formulation, Salix plans to conduct a comparative multi-point dissolution study The multi-point dissolution procedure will be based on the USP methodology for ciprofloxacin In addition, Salix plans to submit the bioequivalence data in support of the approval of the Spanish generic tablet formulation

Ms [redacted] stated that Salix does not currently have any information regarding the results of the bioequivalence study between the Spanish generic ciprofloxacin and the Spanish Bayer ciprofloxacin formulations Salix is, however, in the process of purchasing the report of this bioequivalence study After this report is received and translated, it will be submitted to the Agency Dr Ajayi pointed out that at this point in time, the Agency has no documentation that validates bioequivalence among the Spanish generic ciprofloxacin formulation and the Spanish Bayer ciprofloxacin formulation

Dr Ajayi emphasized that if the Spanish generic ciprofloxacin formulation is found to be bioequivalent to the Spanish Bayer ciprofloxacin formulation using the U S FDA standard, the proposed dissolution profile comparison can be used to link the Spanish Bayer ciprofloxacin formulation to the U S Bayer ciprfloxacin formulation The manufacturing processes, however, must be comparable Therefore, it is important for Salix to provide the Agency with as much information as possible regarding both the components and composition of the Spanish Bayer ciprofloxacin formulation and the U S Bayer ciprofloxacin formulation In addition, Salix should provide information such as comparability of the manufacturing process and equipment used in the manufacture of each formulation Ms [redacted] stated that as Bayer is a competitor of Salix for this indication, obtaining right of reference to Drug Master Files that would contain the requested information might not be feasible It is for this reason that Salix proposed to conduct a comparative multi-point dissolution study using the three formulations to aid in establishing bioequivalence among the three ciprofloxacin formulations

Dr Ajayi recommended that Salix review the Agency's SUPAC-IR document The issue for the Agency is that if products manufactured at different sites are being compared, it needs to be documented how any differences in the manufacturing process affect the drug product It may be the case that due to marked differences in manufacturing processes and equipment, there are differences in bioavailability which dissolution studies alone

could not address However, if the manufacturing processes are very similar, a full dissolution profile should be sufficient to assess bioequivalence

Salix stated that a single media would be used for the dissolution study For analysis of the dissolution data, an F2 similarity factor will be used Although the current — speed of — was based on the solubility of rifaximin, — speeds of — — will be evaluated In addition, the current dissolution specification of NLT — at — may be tightened as more data become available Dr Ajayi stated that the NDA submission should contain a summary of the dissolution development history A pH solubility profile as well as dissolution profiles in different pH and — speeds should be included in this summary

It was agreed that submission of the *in vitro* induction study would not delay submission of the NDA and that the results of the study would be submitted during the course of the NDA review Salix stated that the protocol for the induction study will be submitted to the IND for review

Minutes Preparer _____
Diana Willard

Concurrence, Meeting Chair _____
Funmilayo Ajayi, Ph D

Rough Draft 1/31/01, Final 2/15/00

Concurrence

HFD-880/FAjayi
HFD-880/HMahayni

cc

Division Files
HFD-590/DWillard
HFD-880/FAjayi
HFD_880/HMahayni

DFS Keywords admin minutes

/s/

Diana Willard
2/16/01 07 42 14 AM
CSO

Funmilayo Ajayif
2/16/01 12 02 03 PM
BIOPHARMACEUTICS

Minutes of a Meeting

Meeting Date	January 12, 2001
Application	IND 52,980 rifaximin tablets
Sponsor	Salix Pharmaceuticals, Inc
Subject	Pre-NDA

Attendees

Salix Pharmaceuticals, Inc

Lorin Johnson, Ph D	Senior Vice President, Development and Chief Scientific Officer
Lise Riopel, Ph D	Vice President, Clinical Affairs
John de la Fuente	Director, Quality Affairs

Salix Pharmaceuticals Consultants

	Biopharmaceutics Consultant
	Statistical Consultant

Alfa Wassermann

Ernesto Palazzini, M D	Director, Clinical Research
Miriam Barbanti, Ph D	Head, Pre-clinical Development
	Regulatory Affairs Consultant
	Regulatory Affairs Consultant
	Regulatory Affairs Consultant
	Non-clinical Safety Consultant
	Medical Consultant

FDA

Mark Goldberger, M D , M P H	Division Director, HFD-590
Renata Albrecht, M D	Deputy Division Director, HFD-590
Brad Leissa, M D	Team Leader/Medical Officer, HFD-590

John Powers, M D	Medical Officer, HFD-590
Edward Cox, M D	Medical Officer, HFD-590
Karen Higgins, Sc D	Team Leader/Mathematical Statistician, HFD-725
Cheryl Dixon, Ph D	Statistician, HFD-725
John Smith, Ph D	Chemist, HFD-590
Philip Colangelo, Ph D	Clinical Pharmacology & Biopharmaceutics, HFD-880
Houda Mahayni, Ph D	Clinical Pharmacology & Biopharmaceutics, HFD-880
Shukal Bala, Ph D	Team Leader/Microbiology, HFD-590
Peter Dionne, M S	Microbiologist, HFD-590
Kenneth Hastings, Ph D	Team Leader/Pharmacology, HFD-590
Steve Kunder, Ph D	Pharmacologist, HFD-590
Diana Willard	Regulatory Health Project Manager, HFD-590

Background

This Pre-NDA meeting was requested by Salix Pharmaceuticals, Inc (Salix) to discuss issues regarding their proposed NDA for rifaximin tablets for the treatment of — diarrhea The sponsor submitted a meeting package on December 15, 2000 in preparation for this meeting In addition, a January 3, 2001 facsimile transmission from Salix provided draft efficacy and safety tables from clinical trial RFX-IS-9801 that were requested by Dr Powers

Meeting Objective

The meeting objective was to discuss issues pertaining to the proposed Salix NDA submission for rifaximin for treatment of — diarrhea

Discussion

Following introductions, Salix began by presenting slides (Attachment 1) outlining product background, a summary of the clinical studies, an overview of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), a manufacturing summary, and a discussion of key issues and questions

Summary of Clinical Studies

Slide 10 - In pivotal Study R/C-TD/01 97, rifaximin was administered bid for a head-to-head comparison with the approved dosing regimen for ciprofloxacin In pivotal Study RFX-ID-9801, rifaximin was administered tid Salix stated that as Study R/C-TD/01 97 was nearing completion the decision was made, after much internal discussion, to use tid dosing in Study RFX-ID-9801 Salix believed that a tid regimen

would be more efficacious than a bid regimen due to the poor absorption of the drug The Division thought compliance would be better with bid administration.

Slide 18 - Salix noted that in terms of censoring, the protocol analysis plan stipulated that for treatment failures or withdrawals, the time to last unformed stool would be recorded as 120 hours

Slide 20 - Salix is in the process of preparing a microbiologic response table for Study RFX-ID-9801 similar to the one already prepared for Study R/C-TD/01 97 and presented in Slide 20 There were approximately 10 *Shigella spp* organisms in Study R/C-TD/01 97 and about 15 total *Shigella spp* from the two pivotal studies combined For *Cryptosporidium parvum*, there were over 20 organisms from the two pivotal studies combined and about 10 for *Giardia lambia* For *Salmonella spp* , there were less than a dozen organisms from all three studies combined

Slide 22 – The Division was concerned as to why a poorly absorbed drug should be associated with systemic central nervous system adverse events Salix believes that the observed nervous system disorders were due to dehydration from diarrhea rather than a direct drug effect of rifaximin

Overview of ISE and ISS

Integrated Summary of Efficacy

Slide 25 - Salix stated that Study R-TRDISR/01 96 is a Phase 2 dose-ranging study that also provides supportive information on the bacteriological response to rifaximin

Slide 27 - Salix stated their intent to pool microbiologic response data across studies The rationale for pooling is to obtain an adequate number of organisms to statistically evaluate

Slide 28 - Salix noted that there are some patients who are neither treatment failures nor cures This category would include patients who, on their own, decided that they were feeling better and left the study Final data points for these protocol violators were not collected These patients would be censored but not classified as treatment failures Salix stated that there are a very small number of patients that fall into this category

Integrated Summary of Safety

Slide 30 - Salix stated that if a subject received even one dose of study drug they were included in the database

Slide 37 - Salix clarified that Alfa Wassermann, the innovator for rifaximin, subcontracted with — to manufacture the active pharmaceutical ingredient for the U S trials

FDA Questions

Slide 45 - Salix stated that at some point in time they would like to talk with the Agency regarding the pediatric program for rifaximin Although Salix has licensed from Alfa Wassermann all the formulations of rifaximin currently available, Salix believes that there is additional work to be done for a pediatric formulation

Slide 46 -

Slide 47 - The Division stated that in the NDA submission Salix should make a clear argument for the doses that were chosen to study In addition, any differences in compliance between the tid and bid dosing regimens should be discussed in the NDA Dr Powers noted that information in the medical literature indicates lower compliance rates with tid versus bid drugs

Clinical outcomes as a function of the baseline organism should be presented in the rifaximin NDA If possible, it would be best to present this information for each dose It may be the case, however, that the only organism for which there is sufficient data to present by dose is ETEC

The Division stated that as rifaximin acts luminally it may not be effective against a pathogen that is invasive The question arises whether patients with an invasive pathogen are at increased risk when using rifaximin Data to address this issue are not available in the current database

Slide 48 -

Slide 52 - Salix stated that data from a six month *in vivo* toxicology study in rats indicate that there is no induction of hepatic and intestinal cytochrome P450 Liver homogenate preparations were examined for induction activity at the end of this rat study In addition, a human *in vitro* study to look at inhibition of P450 activity was conducted
Dr Colangelo stated that data from human hepatocytes or liver slices would be the preferred induction data as it is difficult to make predictions in man based on rodent data Salix was referred to an *in vitro* guidance regarding the use of human hepatocytes or liver slices to look at induction activity

Slide 54 - The December 15, 2000 meeting package states that not less than rifaximin is dissolved in Salix stated that more dissolution data would be available as the commercial sites are qualified From these data, dissolution results will be evaluated and a final specification proposed

Concerns from the Clinical Pharmacology and Biopharmaceutics Reviewers included

1 tightening the currently proposed dissolution specification from NLT n

2 poor aqueous solubility of rifaximin and the percentage of dissolution medium, and

3 potential lack of discriminatory power of the currently proposed speed of It was recommended that dissolution be evaluated at lower speeds, i e ,

Salix Key Issues

Slide 55 - Dr Goldberger stated that the following are two key issues with regard to approval of rifaximin for diarrhea

1 what the microbiology data will support in terms of species as well as cure rates within each species of organism and

2 the strength and clarity of the argument regarding how the two pivotal studies support the rationale for the dose selection Salix proposes that the efficacy of the higher dose will support administration of the lower dose this is the opposite of the usual argument

Slide 56 - Dr Colangelo requested that Salix provide the Division with all the currently available information on the three formulations of ciprofloxacin used in the rifaximin clinical trials, U S Bayer ciprofloxacin, Spanish Bayer ciprofloxacin, and Spanish generic ciprofloxacin

Slide 58 - Salix stated that an identical symptom form was provided to investigators for both Studies R/C-TD/01 97 and RFX-ID-9801 For Study RFX-ID-980, investigators were "formally" instructed to report any worsening of symptoms Therefore, more details regarding patient symptoms were collected in Study RFX-ID-980

Dr Powers stated that for the dysentery type diarrhea it would be helpful to submit pooled data as well as present data for each study in the ISE

Slide 59 - The Division noted that any foreign papers submitted in the NDA must be translated to English

Slide 62 - Dr Kunder stated that, at this point in time, there is no need to conduct IV teratology studies

Slide 63 - Mr Dionne stated that 20 isolates for each major pathogen expected in
— diarrhea is probably not a sufficient number for inclusion of MIC data on *in vitro* testing The usual requirement for inclusion on this list in the labeling is 100 isolates from more than one study It is acceptable to include isolates from published data if all the supporting documentation is submitted

Mr Dionne stated that the December 22, 2000 proposed labeling rule published in the Federal Register should have no impact on the proposed rifaximin labeling as the rule will most probably not be finalized in the near future

Mr Dionne stated that if Salix plans to demonstrate that rifaximin is bactericidal, kill curves that include data from 1, 8, and 24 hour time samples should be submitted A 3 log reduction would be considered to be bactericidal

Slide 65 - Salix stated that based upon the results on the *in vitro* data there are currently no plans to conduct any *in vivo* drug interaction studies Even if it is determined that rifaximin induces P450, *in vivo* drug interaction studies probably will not be conducted

due to the poor absorption of the drug The results from both the *in vitro* inhibition and induction studies would need to be reviewed by the Division before any decision can be made regarding the need to conduct *in vivo* drug interaction studies

The Division stated that completion of the *in vitro* induction study should not delay submission of the NDA but the results should be submitted during the course of the review Salix stated that a draft protocol will be sent to the Division for review

NDA Submission

Salix stated that the timeline for submission of the rifaximin NDA is driven by stability batches The current target date for submission is late summer 2001

Summary

Salix presented slides outlining product background, a summary of the clinical studies, an overview of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), a manufacturing summary, and a discussion of key issues and questions

Key issues pertaining to approval of a rifaximin NDA for — diarrhea were discussed The need to validate any supporting data from published studies was emphasized. In addition, microbiology data needed for approval in terms of species as well as numbers within each species of organisms was discussed The Division stated that the strength and clarity of the argument regarding how the two pivotal studies support the rationale for the dose selection is an important aspect for the rifaximin NDA

Minutes Preparer _____
Diana Willard

Concurrence, Meeting Chair _____
Mark Goldberger, M D , M P H

25 Page(s) Withheld

/s/

Mark Goldberger
4/16/01 12 27 58 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogen
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE. 1 October 1999

TO ——
Regulatory Consultant

ADDRESS· Salix Pharmaceuticals, Inc
3600 West Bayshore Road, Suite 205
Palto Alto, California 94303
Phone (650) 849-5922
Fax (650) 856-1555

FROM: Brenda J Atkins, Regulatory Project Manager

IND/DRUG 52,980 (Serial No 026)/Rifaximin

SUBJECT: **FDA comments on clarification of September 21, 1998 meeting minutes**

Please refer to your IND submission dated August 9, 1999, received August 12, 1999, under serial number 026, containing clarifications to meeting minutes (refer to Serial #011 dated October 20, 1998) prepared as a result of the face-to-face meeting with Salix Pharmaceuticals' representatives on September 21, 1998 We have completed our review of this submission and have the following comments on items #2 and #3 under **"Clarification of Minutes of September 21, 1998 Meeting"** The items are duplicated below and our responses are italicized.

2 In vitro studies on the induction/inhibition of liver microsomes/hepatocytes by rifaximin and major metabolites of rifaximin will be conducted using animal (rat) tissue and not human tissue as stated in the meeting minutes (refer to page 6 of attachment minutes)

FDA Response

In vitro study on induction/inhibition potential has to utilize human tissue because of differences in the expression of the CYP450 enzymes in rats and human.

3 The NDA will include data on urinary metabolite levels in humans. However, this information has been collected separately from the food-effect study (refer to page 6 of attached minutes

FDA Response

Although urinary levels are not generally a requirement in food-effect study, because of the low bioavailability/absorption of rifaximin following oral dosing which will yield extremely low levels of rifaximin in plasma, measuring urinary level of the metabolites of rifaximin under fed/fast can be another method of evaluating changes in systemic exposure of rifaximin under fed conditions. This type of food-effect study use high fat meal. Please refer to draft food-effect guidance on the web (www.fda.gov). It is recommended that you submit a protocol for these studies for review prior to initiation of the studies.

Please feel free to contact me on (301) 827-2127 if you have any questions regarding the contents of this transmission or if further discussions are needed via a teleconference.

/S/

Brenda J Atkins, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

Attachment 4 January 10, 2001 fax from FDA concerning question for the January 12, 2001 Pre-NDA meeting

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE I

FACSIMILE TRANSMITTAL SHEET

DATE May 11, 2004

To —	**From** Andrei Nabakowski
Company Salix Pharmaceuticals Inc	Division of Special Pathogen and Immunologic Drug Products
Fax number —	**Fax number** 301 827-2475
Phone number —	**Phone number** 301-827-2127
Subject Rifaximin Labeling Comments	
Total no of pages including cover 3	
Document to be mailed • YES	☑ NO

Please refer to NDA 21-361/Rifaximin for travelers' diarrhea, and to your submission dated April 21, 2004 which provided proposed container labeling We have the following comments on this labeling

A — LABEL

B CONTAINER LABEL

Also, as previously discussed by telephone, DMETS and the Division have approved the use of the name "Xifaxan" as a trade name for rifaximin

Please contact me at (301) 827-2127 if you have any questions regarding this facsimile transmission

Andrei E Nabakowski, Pharm D Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Andrei Nabakowski
5/11/04 05 02 35 PM
CSO
NDA 21-361/Rifaximin

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE March 11, 2004

To	**From** Andrei Nabakowski
Company Salix Pharmaceuticals Inc	Division of Special Pathogen and Immunologic Drug Products
Fax number	**Fax number** 301 827-2475
Phone number	**Phone number** 301-827-2127

Subject 03/11/04 Rifaximin comments

Total no of pages including cover 3

Document to be mailed • YES ☑ NO

Please refer to NDA 21-361 for rifaximin tablets Our chemistry reviewer has the following comments and requests

1) The ICH Q3B guidance recommends the use of terms "any unspecified degradation product" and "total degradation product" for individual unknown impurities and total impurities Please revise your drug product impurity specification nomenclature as per the recommended terminology

2) As you have stated that the HPLC method — will be used for drug product Assay only, you should make changes to the title and contents of the procedure by deleting all references to the related substances to show that this method is used only for the Assay

3) Since the drug product Assay, related substance determination and dissolution methods have changed from the originally submitted methods, please submit three copies of the updated methods validation packages

4) The dissolution acceptance criterion of NLT — (Q = —) at — require sample to be taken at — However, the submitted dissolution method — requires samples to be taken out at — minutes The calculations for the amount dissolved include corrections for the samples taken at various time points Please explain why the method does not direct the operator to sample only at — and calculate amount of rifaximin dissolved using simple formula for single point calculation

Please contact me at (301) 827-2127 if you have any questions regarding this facsimile transmission

Andrei E Nabakowski, Pharm D Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Andrei Nabakowski
3/11/04 06 46 12 AM
CSO
NDA 21-361/Rifaximin

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE January 21, 2004

To	**From** Andrei Nabakowski
Company Salix Pharmaceuticals Inc	Division of Special Pathogen and Immunologic Drug Products
Fax number	**Fax number** 301 827-2475
Phone number	**Phone number** 301 827-2127
Subject Case report forms from Goa, India site	
Total no of pages including cover 3	

Document to be mailed • YES ☑ NO

We have the following request regarding your November 25, 2003 resubmission for NDA 21-361/rifaximin tablets

Please submit the case report forms from Study RFID3001 for those subjects in Goa, India who were censored and for whom you are missing diary data If possible, please submit this information electronically on cd-rom

Please contact me at (301) 827-2127 if you have any questions regarding this facsimile transmission

Andrei E Nabakowski, Pharm D Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Andrei Nabakowski
1/21/04 02 36 14 PM
NDA 21-361/Rifaximin Case Report Form Request

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE January 14, 2004

To	**From** Andrei Nabakowski
Company Salix Pharmaceuticals Inc	Division of Special Pathogen and Immunologic Drug Products
Fax number	**Fax number** 301 827 2475
Phone number	**Phone number** 301-827-2127
Subject Micro table	
Total no of pages including cover 4	
Document to be mailed • YES	☑ NO

Regarding your November 25, 2003 resubmission for NDA 21-361/rifaximin tablets, our microbiology reviewers have the following request

Please submit the data for study RFID3001 "A Randomized, Double-Blind, Multi-Center, Comparative Study of Rifaximin vs Placebo vs Ciprofloxacin (Cipro®) in the Treatment of Travelers' Diarrhea Due to Enteropathogenic Organisms" in a table with the following format